

SUMMARY MINUTES OF THE

GENERAL AND PLASTIC SURGERY DEVICES PANEL OF THE

MEDICAL DEVICES ADVISORY COMMITTEE

OPEN SESSION

JUNE 16, 1999

Gaithersburg Hilton, Salons C, D, and E
620 Perry Parkway
Gaithersburg, Maryland

GENERAL AND PLASTIC SURGERY DEVICES PANEL ROSTER
June 16, 1999

Thomas V. Whalen, M.D.
Acting Chair

Benjamin O. Anderson, M.D.
Voting Member

Maxine F. Brinkman, R.N.
Consumer Representative

James W. Burns, Ph.D.
Industry Representative

Phyllis Chang, M.D.
Voting Member

Michael D. Crittenden, M.D.
Deputized Voting Member

David L. DeMets, Ph.D.
Voting Member

Nancy N. Dubler, LL.B.
Deputized Voting Member

Thomas B. Ferguson, M.D.
Deputized Voting Member

Susan Galandiuk, M.D.
Voting Member

Blake Hannaford, Ph.D.
Deputized Voting Member

Mark A. Talamini, M.D.
Deputized Voting Member

Cedric F. Walker, Ph.D., P.E.
Deputized Voting Member

FDA Personnel

David Krause, Ph.D.
Panel Executive Secretary

Celia Witten, Ph.D., M.D.
Director, Division of General and Restorative Devices

James Dillard
Deputy Director, Division of General and Restorative Devices

Stephen P. Rhodes
Chief, Plastic and Reconstructive Surgery Devices Branch

Larry G. Kessler
Director, Office of Surveillance and Biometrics

Dwight Yen, M.S.
Lead Reviewer, Division of General and Restorative Devices

Roxolana Horbowyj, M.D.
Medical Officer, Division of General and Restorative Devices

Harry F. Bushar, Ph.D.
Statistician, Division of Biostatistics

OPEN SESSION

The meeting was called to order at 10:07 a.m. **Dr. David Krause, Panel Executive Secretary**, read appointments to temporary voting status for Drs. Crittenden, Dubler, Ferguson, Hannaford, Talamini, and Walker and an appointment as acting chair for Dr. Thomas Whalen. Dr. Krause also read the conflict of interest statement, noting that matters concerning Drs. Walker, Hannaford, Galandiuk, and Anderson had been considered but their full participation allowed.

Acting Chair Dr. Thomas Whalen noted that the panel would be discussing a premarket approval application (PMA) for Intuitive Surgical Incorporated's Surgical Endoscopic Instrument Control System and Endoscopic Instruments. He asked the panel members to introduce themselves.

Stephen P. Rhodes, Chief of the Plastic and Reconstructive Surgery Devices Branch, gave the branch update since the last panel meeting. He stated that the panel had recommended classifications for five wound dressings at its November meeting. The FDA is preparing a Final Rule for four of them to be classified as Class I, Exempt: gauze, hydrogel, occlusive, and hydrophilic, all of which have no biologic or animal source material. Classification of the fifth, porcine dressings, is still under consideration. The Plastic Surgery Branch has also developed a guidance document on surgical meshes and is updating guidances on breast implants, wound dressings, and non-interactive wound dressings. It is developing a new guidance on sutures. The branch is preparing a Final Rule requiring the submission of PMA applications for saline-filled breast implants, which should be completed this year.

Larry G. Kessler, director of the Office of Surveillance and Biometrics, gave the panel a presentation on postmarket surveillance and methods of postmarket evaluation at the Center for Devices and Radiological Health. He explained that medical devices have a definable life cycle, in which the clinical community has an important role to play in providing feedback during postmarket evaluation. He outlined the questions assessed in the postmarket period and described the Medical Device Reporting (MDR) Program, which provides limited but critical information to FDA about devices with problems, and he listed the possible actions prompted by such a medical device report. Dr. Kessler discussed the two postmarket authorities, postmarketing surveillance and postapproval authority, and outlined the criteria for a panel to suggest postmarketing surveillance as well as study designs used in postmarketing surveillance. He acknowledged the frustrations involved in monitoring the postmarketing period and challenged the advisory panel to ensure that a postmarketing study will be of primary importance, to specify the public health question it is to address, and to note what will be done with the data collected. He briefly outlined of the future for the MDR and Postmarketing Surveillance programs, noting that sentinel reporting will begin using a sample of user facilities committed to reporting and providing regular feedback on device performance.

Mr. James Dillard, Deputy Director of the Division of General and Restorative Devices, presented outgoing panel member James W. Burnes with a plaque honoring his service to the panel.

OPEN PUBLIC HEARING

There were no requests to speak.

OPEN COMMITTEE DISCUSSION

Sponsor Presentation

Mr. Michael Daniel, vice president for regulatory/clinical affairs of Intuitive Surgical Inc. (ISI) began the PMA sponsor application for the device, **Intuitive Surgical Endoscopic Instrument Control System and Endoscopic Instruments**, with a brief history of the company and of the device's regulatory status.

Dr. Fred Moll, the company's medical director, described the device technology and discussed computer-assisted surgery.

Dr. Dan Bloch of Stanford University gave a statistical analysis of the clinical trial, which consisted of two separate studies based on prospectively randomized, concurrently controlled clinical equivalence trials.

Dr. Barry Gardiner, principal investigator, discussed the clinical study results. He explained the study design, which included use of the device in a total of 245 laparoscopic cholecystectomy and Nissen fundoplication procedures over a three-month trial in Mexico. The study objective was to demonstrate device equivalence in safety and effectiveness to the control of standard laparoscopic equipment in performance of general laparoscopic tasks, including grasping, cutting, blunt and sharp dissection, approximation, ligation, electro-cautery and suturing. Dr. Gardiner described both procedures and discussed inclusion and exclusion criteria for the study, as well as primary and secondary endpoints for safety and effectiveness. These endpoints included the conversion rate of device to conventional tools or of control to open technique, procedure duration, postoperative hospital stay, safety measures such as blood loss, bile leak, and dysphagia, and DeMeester and Psychological Well-Being Scores at 30 days. He

gave an overview of 9 procedure-related complications out of the 245 procedures and discussed each complication. Dr. Gardiner provided additional clinical observations on postoperative dysphagia, intra-operative blood loss and gall bladder rupture or spillage.

Questions from panel members to the sponsors included the need for special cleaning instructions, the need for scrubbed surgical back-up in the operating room, and the learning curve for surgeons.

The Open Session was adjourned at 12:35 p.m. for lunch, followed by a Closed Session at which sponsors presented proprietary material to the panel. It resumed at 2:00 p.m.

FDA Presentation

Dwight Yen, FDA lead reviewer for the PMA, summarized the device's regulatory history and described the device as consisting of a surgeon's console, patient table side surgical cart, and a system control unit. He reported no issues arising from engineering tests on hardware, software, performance, material biocompatibility, sterility, and standards compliance. Performance testing included hysteresis, animal, cadaver, in vitro suturing, and feasibility studies, as well as the clinical trial. Mr. Yen analyzed system reliability, reporting that three system faults resulted in a 12-13 minute delay in two cases and a 20-minute delay in the third. Fail-safe procedures caused the system to enter the appropriate error landing state without uncontrolled motion, and the system was restarted to complete the procedures.

Dr. Roxi Horbowyj, medical officer, discussed the FDA's clinical perspective on the device, which allows surgical tasks to be performed with software assistance through three ports for the surgeon's hands and the laparoscope, in conjunction with

conventional laparoscopic instruments for any additional ports and non-ISI system adapted tools. She reviewed material already presented by the sponsors about the clinical study in terms of objective, design, procedures, endpoints, sample size determination, target population, and outcomes. Postoperative outcomes showed control and investigational device study populations to be clinically comparable for adverse events rates, Psychological Well Being Scores and DeMeester scores at 30 postoperative days, and postoperative length of hospital stay. Procedure duration and estimated blood loss were greater for investigational device than for control.

Dr. Horbowyj concluded that ability to perform surgical tasks with investigational and control devices in laparoscopic cholecystectomy and laparoscopic Nissen fundoplication was demonstrated in the study population for grasping, blunt dissection, cautery dissection, suture tie placement around tubular structures, needle suture placement, and suture tie for tissue approximation. She noted that unexpected system shutdown into safe mode occurred, requiring active engineering intervention and system modification. Dr. Horbowyj suggested that increase in procedure duration and variability in estimated blood loss of investigational device procedures compared to control may be attributable to surgeon/surgical team position on the learning curve for device use. Non-device-failure-associated conversions of two laparoscopic cholecystectomies from investigational device to control device were also attributed to learning curve issues. There were no conversions due to device software or hardware failure.

Harry Bushar, statistician, presented the FDA statistical review. He described the clinical trial procedures and design and defined the objective of statistical equivalence testing. Mr. Bushar explained the null and alternative hypotheses for the statistical

equivalence test and defined the clinical endpoints or deltas for primary and secondary effectiveness outcomes and safety outcome. With the exception of the hospital stay during the laparoscopic cholecystectomy, statistical equivalence was not demonstrated. He suggested that deltas may be increased, if clinically feasible, or the sample sizes per group may be increased in an attempt to establish statistical equivalence.

Panel Member Dr. Blake Hannaford gave the panel preclinical review. He discussed remote manipulation technologies, summarizing their history and bilateral tele-operator technical issues to be addressed such as mechanical design, usability, and control properties. He listed performance questions for consideration and defined stability and its link to safety. Dr. Hannaford then discussed the ISI System and classified it as a bilateral, impedance-controlled force-reflecting tele-operator. He concluded that it warranted only a moderate level of concern because the hardware is designed to perform envelope checking. He listed as issues for concerns the instability manifested in some videos, the lack of documentation on stability margins or instability incidence, and the absence of specifications and analysis testing on the control system. He suggested documentation on five technical issues: control equations, control system stability analysis, test data validation, gain values used in production, and documentation of tremor filtering.

Panel Member Dr. Mark Talamini gave the panel clinical overview. He mentioned the advantages and disadvantages of laparoscopic surgery and differentiated between the two procedures used in the trial in terms of difficulty, noting that laparoscopic surgery is ideal for highly technical operations. He listed as key study indicators the learning curve effect on procedure time, blood loss, and complication rates.

Dr. Talamini stressed the importance of the video data he had observed in evaluating the application and stated that he saw precise motions, an ability to precisely control bleeding, an ability to gently dissect tissues, enhanced knot tying, and a similarity to hand motions. He thought that physician training was not a relatively large issue.

Panel Member Dr. David DeMets gave the panel statistical overview. He stated that the problem of determining equivalence versus an active control is a very challenging problem compared to determining superiority because of the need for adequate power to detect the delta. He suggested the need for an agreed scale of reference, either absolute or relative and binomial or continuous. The process should begin by defining the question in terms of what the desired outcome should be. An absolute or relative scale should be selected, as should a minimum delta based on clinical considerations. The trial should be sized accordingly and the results presented with confidence intervals. He suggested that on the current application, the learning curve was not long enough and urged that future deltas should be selected on the basis of being clinically meaningful.

Panel questions in discussion concerned the indications for intended use, the list of instruments considered as part of the system, and the possible use of the system for coronary bypass or cardiac procedures. Mr. Dillard of the FDA clarified that the FDA does not wish to look at new technologies procedure by procedure but is looking at general surgical procedures while requiring more specific data for more specific procedures. Some panel concern was expressed over the advisability of approving costly new technologies without measurable benefit, but it was noted that by regulation, the basis for device approval rests upon safety and equivalence, not cost considerations.

FDA Questions

Mr. Yen read the FDA questions to the panel.

The panel concluded that the data have largely demonstrated safety and effectiveness in terms of clinical versus numeric equivalence. The preponderance of panel opinion was that the net risk/benefit ratio favors the proposed device, with an important ethical disclaimer on concerns about the cost of new technologies for undetermined additional benefits.

The panel had no particular concerns regarding use of the device in general surgical populations, suggesting that the considerations listed in terms of vulnerable populations were clinical decisions and practice-of-medicine issues outside the FDA's area of regulatory concern.

On adequacy of proposed safeguards for device use, the panel disliked use of the term "failsafe," noting that nothing is 100% safe. Panel members did think that adequate safety measures were built into the device hardware and software.

The panel recommended that training should include failure mode and failsafe procedure training for all members of the operating team. Didactic and inanimate training was recommended as an important component that should precede training with human subjects. A formal training proposal should be part of the application, although the panel did not specify the number of hours needed. Several members urged that a gowned and sterilely gloved surgeon should always be in the room in case of emergency during the procedure.

OPEN PUBLIC HEARING

There were no requests to speak from members of the audience, the sponsor team, or the FDA.

PANEL VOTE

Executive Secretary Dr. Krause read the panel voting instructions. A motion was made and seconded to recommend the application for approval subject to the following conditions: 1) that the sponsors supply the outline of a best case training protocol; 2) that the device be labeled as a product equivalent to control with no reference to clinical benefit; 3) that the clip applier be removed from the specified list of instruments because it had not been sufficiently tested; 4) that a gowned and sterile-gloved surgeon be in the operating room at the console. After discussion, this motion was defeated.

A motion was then made and seconded to recommend the application for approval subject to the following conditions: 1) that the clip applier be removed from the list of specified instruments and 2) that the sponsors provide a detailed description of the training they endorse for use of their product. This motion was passed, with one member (Dr. DeMets) opposed on the grounds that the product did not meet the criteria for effectiveness and equivalency. All other voting members stated that they voted to recommend the application for approval on the grounds that safety and effectiveness had been demonstrated, with several saying they saw potential for interesting future applications of the technology.

The chair thanked all those present and adjourned the session at 4:45 p.m.

I certify that I attended the Open Session of the General and Plastic Surgery Devices Panel Meeting on June 16, 1999, and that this summary accurately reflects what transpired.

A handwritten signature in cursive script, reading "David Krause".

David Krause, Ph.D.
Executive Secretary

I approve the minutes of the meeting as recorded in this summary.

A handwritten signature in cursive script, reading "T. V. Whalen".

Thomas V. Whalen, M.D.
Acting Chair

Summary minutes prepared by Aileen M. Moodie
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